IJPSR (2020), Volume 11, Issue 8 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 26 October 2019; received in revised form, 29 February 2020; accepted, 19 April 2020; published 01 August 2020

IMPROVEMENT IN BIOAVAILABILITY OF POORLY SOLUBLE DRUG BY SELF MICRO EMULSIFYING DRUG DELIVERY

Aniket Shelar [1], Jayashri Mahore [*1], Sanjeevani Deshkar [1] and Rashmi Trivedi [2]

Department of Pharmaceutics [1], Dr. D. Y. Patil Institute of Pharmaceutical Sciences and Research, Pimpri, Pune - 411018, Maharashtra, India.
Smt. Kishoritai Bhoyar College of Pharmacy [2], New Kamptee - 441002, Maharashtra, India.

Keywords:

Self micro-emulsifying drug delivery system, Microemulsion, Lipids, Surfactants

Correspondence to Author:
Jayashri Mahore

Assistant Professor,
Department of Pharmaceutics,
Dr. D. Y. Patil Institute of Pharmaceutical Sciences and Research, Pimpri, Pune - 411018, Maharashtra, India.

E-mail: jayashri_mahore@rediffmail.com

ABSTRACT: Solubility is the rate-limiting step for bioavailability of poorly water-soluble drugs. The solubility of poorly water-soluble drugs can be enhanced by incorporating active pharmaceutical ingredients into oral lipid-based drug delivery systems. Self micro emulsifying drug delivery system (SMEDDS) is a researcher's choice amongst other oral lipid drug delivery systems because it offers advantages like simplicity to manufacture, convenience in scale-up, less interference of food on the dosage form and has the capability to deliver peptides. SMEDDS acts as a drug delivery carrier in which a broad range of different drug moieties can be incorporated. The bioavailability of lipophilic drugs can be significantly increased by formulating in the SMEDDS form. The present review provides a comprehensive summary for types of SMEDDS, manufacturing process, formulations aspects, evaluation characteristics, and patents registered on account of oral lipid drug delivery system.

INTRODUCTION: Insufficient aqueous solubility results in poor bioavailability, high intra and inter-subject variability, lack of dose, gastric, and enzymatic drug degradation. About 40-70% of all newly discovered drugs experience the same limitation while entering in drug development. Micronization of solids, preparation of solid dispersion, salt formation, nanoparticles, or conversion of API to lipid-based drug delivery systems are some majors used to formulate a drug delivery system of poorly water-soluble drugs.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.11(8).3595-07

The article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.11(8).3595-07

Among all the lipid-based formulations, self micro emulsifying drug delivery systems have attracted the researchers significantly in improving the oral bioavailability of poorly water-soluble drugs [1, 2].

Self-Micro Emulsifying Drug Delivery System (SMEDDS): SMEDDS are made up of oil, surfactants, and co-surfactants and defined as physically stable, isotropic mixtures of natural or synthetic oil, solid or liquid surfactant and solubilized drug substance. Gentle agitation of GIT facilitates SMEDDS to self emulsify. Small droplet size between 100 - 250 nm provides a large interfacial area, which ultimately enlarges the activity of pancreatic lipase, which acts by hydrolyzing triglycerides and ultimately promotes the faster release of a drug. SMEDDS get absorbed through the lymphatic pathway, thereby pass hepatic metabolism.

The solid SMEDDS increases the stability of formulation as compared to that in the emulsion form, which leads to reduced gastric irritation and thus increases the patient compliances. Oils, surfactants, and co-surfactants of SMEDDS play a critical role in increasing the bioavailability of SMEDDS. Surfactant helps to improve bio-availability by keeping the drug in solution form and disturbing lipid bilayer structure, which avoids the drug dissolution and ultimately enhances permeation. Oil droplets facilitate the uniform distribution of the drug and reduce the irritation by minimizing contact between drug and gut wall. The addition of lipid imparts protection to the drug from enzymatic and chemical degradation with activation of lipoproteins, which promotes lymphatic transport of lipophilic drugs. SMEDDS are physically stable when analyzed with emulsions, which are sensitive and unstable dispersed forms. An increase in bioavailability with more reproducible blood time profiles can be exhibited by the lipophilic drug by formulating in SMEDDS form compared to conventional emulsion [3]. The advantages and disadvantages of SMEDDS are enlisted in **Table 1**.

Filling of prepared SMEDDS in soft and hard gelatin capsules resulted in leakage and difficulty in manufacture. Therefore, the conversion of liquid SMEDDS to solid- SMEDDS (S-SMEDDS) by adsorbing SMEDDS on inert carrier can be employed to overcome the manufacturing problem, leakage problem and can also extend the shelf life of the drug. Conversion of free-flowing powders to tablets or capsules enhances the acceptability of dosage form by patients. Oral lipid-based drug delivery system (OLDDS) basically comprises three different types; Self emulsifying drug delivery system (SEDDS), Self Micro emulsifying drug delivery system (SMEDDS), and Self nano emulsifying drug delivery system (SNEDDS). SEDDS, SMEDDS, and SNEDDS are categorized as emulsions with a size range of 200 nm – 5 µm, <100 nm, and 20 nm – 100 nm, respectively [4].

TABLE 1: ADVANTAGES AND DISADVANTAGES OF SMEDDS

Advantages	Disadvantages
Improved oral bioavailability	Release depends on digestion
Simple manufacture and scale-up process	Lack of predictive *in-vitro* models for evaluation
Minimizes Intersubject and intrasubject variability	Need to incorporate a high concentration of surfactant can inflame GIT
Less interference of food	
Prevent enzymatic hydrolysis of peptides [28, 29]	
No effect of the lipid digestion process	
Lipid drug delivery system increases drug loading capacity	
Improved Stability	
Enhanced Compliance	

Classification of Lipids used in OLDDS: Lipids are classified into different types depending upon use in OLDDS appropriately for poorly water-soluble and lipophilic drugs. It consists of single or pooled excipients, forming oily formulations, SEDDS, and SMEDDS and micellar solutions. The ability to withstand with the dilution, the capability to prevent drug precipitation and compositions of the delivery system, are used to classify lipids into various systems [5].

Type I: Type I system consists of mainly oils *i.e.*, without surfactants. Type I lipids aid drug transfer into the colloidal aqueous phase and facilitate the amphiphilic lipid digestion by pancreatic lipase/ co-lipase. In type I, triglycerides composition consists of 100%, with coarse particle size. The advantage of this system is that the excipients which are utilized in this system are generally regarded as safe (GRAS), simple, and compatible for solid dosage forms such as capsules. However, the disadvantage associated with this system is poor solvent capacity unless the drug is highly lipophilic.

Type II: Type II system consists of isotropic mixtures of lipid and lipophilic surfactants which have the ability to self emulsify and to form fine o/w emulsions when introduced in aqueous media. Surfactant concentration above 25% (w/w) causes self emulsification which can be increased to 50-60% (w/w). Digestion of SEDDS starts after contact with the gastrointestinal tract. To formulate convenient unit dosage forms of the drugs with

poor aqueous solubility, formulated SEDDS could be encapsulated into hard or soft gelatine capsule [6].

Type III: Type III includes a particle size range between 50-100 nm. In this type, mainly propylene glycol, polyethylene glycol, and ethanol with HLB value greater than 12 are used. Type III is mainly used for the formulation of SMEDDS and further classified as Type IIIA and Type IIIB. These systems are made up of water-miscible excipients with self-emulsifying and wetting properties. Formulation components decide the extent of dispersion and micellization of lipophilic APIs after digestion enhances solubilization.

Type IV: In recent trends, only water-soluble surfactant and hydrophilic co-solvents are used with little or without oil. After gentle agitation in GI fluid, type IV can form transparent micellar solutions. Due to the absence of oil, solvent capacities of type IV can be compromised upon dilution. The nature of composition decides the extent of digestion and ultimately affects drug solubilization and absorption [7].

Biopharmaceutical Aspects: An extensive literature survey explains that the use of lipid increases the bioavailability by depleting gastric transit and thus increasing gastric resistance time [8]. Enhanced secretion of bile salt (BS) with endogenous biliary lipids consisting of phospholipids (PL) and cholesterol (CH) promotes the formation of BS/PL/CH intestinal mixed micelles, which enhance the solubility of GI fluid and ultimately increase the solubility of the poorly water-soluble drug. The addition of exogenous lipids in bile salts swells the micellar structure and enhances the solubilization capacity [9].

In SMEDDS formulations, the drugs which are having high lipophilic nature can bypass the lymphatic transport and enhance the bioavailability directly or by decreasing first-pass metabolism [10]. The drugs which are classified under an anticancer category such as epirubicin, paclitaxel are pumped out by P-glycoprotein (P-gp) from tumor cells. (P-Glycoprotein is multidrug resistance protein1, exhibit in the small intestine under normal physiological conditions.) An increase in uptake of lipid-based drug delivery systems can be attributed to inhibition of P-glycoprotein drug efflux. Coordination of P-gp and cytochrome P450 (CYP3A4) activity may reduce the enterocyte metabolism of a drug.

Cremophore EL, labrasol, Polysorbate 80, polysorbate 20, and TPGS (d-α- tocopheryl polyethylene glycol 1000 succinate) are some examples of surfactants with P-gp inhibitory activity. Improved permeability of poorly water-soluble drugs formulated into SEDDS can be attributed to lipids, lipid digestion products, and surfactants which change the physical barrier function of the gut wall [11, 12].

The presence of lipids in SMEDDS alters the biopharmaceutical characteristics of the drug with reproducible pharmacokinetic behavior [13].

The Need for Self Micro-emulsifying Drug Delivery System: Discovery of BCS class II drugs, *i.e.,* drugs with low solubility and high permeability, results in poor bioavailability. The bioavailability of such drugs can be increased by improving solubility. Solubility can be improved by the pre-dissolution of such drugs into a suitable solvent to overpass the rate-limiting step of solubilization.

But this kind of formulation approach can lead to crystallization in the polymer matrix because of a thermodynamic stable state achieved in the formulation.

Mode of Action of SMEDDS for Drug Absorption: Emulsification occurs when the free energy (ΔG) is negative. The free energy of the conventional emulsion is a direct function of the energy needed to create a new surface between the oil and water phase and can be outlined by the equation-

$$\Delta G = \Sigma N \pi r2 \sigma$$

Where, N --- Number of droplets, r --- Radius of droplets, σ --- Interfacial energy, ΔG --- free energy associated with the process

The two phases of emulsion separate with time to decrease the interfacial area, these emulsions can be further stabilized by emulsifying agents, which form a monolayer of emulsion droplets and hence reduce the interfacial energy and provide a barrier to prevent coalescence [14].

The Composition of SMEDDS Formulation:

Drug: SMEDDS is a choice of formulation for the drug with high lipophilicity and low dose. The solubility of the drug in the oil phase decides the performance of the SMEDDS as the drug should remain in solubilized form. Drugs with low lipid solubility and high doses are unsuitable for SMEDSS formulation. If a high dose of the drug is soluble in one of the components of the SMEDDS, particularly oil, then it can be formulated into SMEDDS.

Preferable drug for SMEDDS is one with a low dose and with log P greater than 5 [15, 16]. SMEDDS formulation mainly comprises of drug, oil, surfactant, and co-surfactant, respectively. Literature updates for ingredients used in the formulation of SMEDDS are updated in **Table 2**.

Oils: Oils used to formulate SMEDSS are mainly a mixture of triglycerides with different fatty acid chain lengths and degrees of unsaturation. Being fully digestive and good absorption ability, triglycerides of vegetable oils are considered as safe. Triglycerides with 6–12 carbon chain (medium-chain triglycerides *i.e.* MCT) containing carbon atoms between 6 and 12 are directly transported by portal blood to the systemic circulation. High solubilization property and resistance to oxidation credited for the wide use of MCT. Whereas, long-chain triglycerides (LCT) possessing carbon atoms greater than 12 are transported *via* intestinal lymphatics [17].

Surfactants: Surfactants are generally ionic, non-ionic or amphoteric. Surfactants stabilize the internal phase and mainly concentrate on the oil-water interface. HLB value and concentration of surfactants are important parameters required to be considered while selecting surfactants. Amongst ionic, non-ionic, and amphoteric surfactants, the nonionic surfactants are preferable because of their good cutaneous tolerance and less toxicity. Surfactants contribute to the enhancement of bioavailability by increasing intestinal permeability or by increasing affinity between intestinal membrane and lipids. The mechanism of action for surfactants is based on their partitioning into the cell membrane as well as disruption of the structural organization of lipid bilayer, which results into enhanced permeation [18].

Co-surfactant: Optimum SMEDDS formulations require a high concentration of surfactants to reduce interfacial tension, but the use of a high concentration of surfactants is not recommended because of their toxicity issues. Therefore, the use of a co-surfactant is suggested to cut down the concentration of the principle surfactants. The flexibility of the interfacial layer can be improved by the addition of co-surfactants. Short to medium chain length alcohols (C3–C8) are most commonly employed as co-surfactants. Some nonionic co-surfactants such as polyoxyethylene alcohol ether are also used because they are less irritant. Medium-chain alcohols such as pentanol and hexanol are partially effective as co-surfactants but high irritation [19, 20].

Formulation of SMEDDS: SMEDDS formulation consists of the following steps

- Selection of oil, surfactant, and co-surfactant.
- Selection of micro-emulsion region by the construction of pseudo-ternary phase diagram.
- Formulation of SMEDDS.
- Evaluation of prepared SMEDDS.

Screening of Excipients:

- **Solubility Study:** The solubility of drugs is determined in different oils, co-surfactants, and surfactants. An excess quantity of the drug is added in 2 ml of each of the selected oil, co-surfactants, and surfactants taken in 5 ml vials separately and are mixed by vortexing for 10-15 min. Further, the vials are then kept at 37 ± 2 °C in an isothermal water bath shaker for 48 hours to reach an equilibrium of mixture. Remove the equilibrated samples from shaker and centrifuge at 3000 rpm at 15-20 min. The obtained supernatants are filtered through Whatman filter paper. The absorbances of this solution are noted using UV-spectrophotometer, and drug concentration is calculated with respect to particular oils, co-surfactant, and surfactants [21].

- **Initial Screening of Surfactants and Co-surfactants:** The emulsification capability of various surfactants and co-surfactants for selected oils are screened by mixing the equal

proportion of selected oils as well surfactants, the mixture is heated gently for 40-50 °C for 1-2 min and allowed for vigorous uniform homogenization. Further, this mixture is added into double distilled water to observe; the number of flask inversions needed to form a homogenous emulsion, and this provides inference about ease of emulsification. The resulted micro-emulsion should be tested for percentage transmittance, turbidity, and clearance. Selection criteria for surfactants are dependent on the efficiency of surfactants for higher emulsification, which exhibit higher percentage transmittance. A similar procedure is carried out for the selection of co-surfactant [22].

Construction of Pseudo-ternary Phase Diagram: SMEDDS is prepared by using two methods; phase inversion temperature method, constructing a pseudo-ternary phase diagram [23].

- **Phase Inversion Temperature Method:** The development of o/w or w/o SMEDDS is dependent on temperature ranges.

- **Construction of Pseudo-ternary Phase Diagram:** To recognize better emulsification region of oil, surfactant and co-surfactant combination ternary phase diagram is essential. The ternary phase diagram of surfactant, co-surfactant, and oil will plot each component of them, which presents an apex of the triangle. Two methods that are used to plot ternary phase diagrams are the Dilution method and Water titration method.

- **Dilution Method:** Ternary mixtures with the different constitutions of surfactant, co-surfactant, and oil are constituted. The different concentrations of surfactant are taken in the range from 30 to 75% (w/w), the co-surfactant concentrations are taken from 0 to 30%, and oil concentration is taken in the range from 25 to 75%. For a particular mixture, the total of oil, surfactant, and co-surfactant concentration should always add to a total of 100%. Here, for example, in the experiment first mixture will be composed of 75% of a surfactant, 25% of an oily phase, and 0% of co-surfactant. As the concentration of co-surfactant increases, the surfactant concentration needs to decrease accordingly to balance a total of 100% of oil, surfactant, and co-surfactant concentration. About a total forty two such mixtures with different concentrations can be formulated. On the basis of demand, the percentage of surfactant, co-surfactant, and oil can be decided. Compositions are examined for nano-emulsion formation by diluting a proper total mixture with double-distilled water. By using spectroscopy techniques, the globule size of the dispersion is evaluated. Dispersions particular having globule size 200 nm or below are considered as advantageous. The area of micro-emulsion or nano-emulsion preparation in the ternary phase diagram is recognized for the respective system in which nano-emulsion or micro-emulsion with desired globule size is observed [24].

- **Water Titration Method:** The construction of the pseudo-ternary phase diagram is conducted by titration of uniform liquid mixtures of surfactant, oil, and co-surfactant with water at room temperature. The oil phase, surfactant, and co-surfactant (surfactant: co-surfactant ratio like 1:1, 1:2, 2:1, 3:1) are developed in the different compositions ranges from 9:1 to 1:9 and weighed in the similar screw-cap glass tubes and are vortexed. Later on, each mixture is slowly titrated with aliquots of distilled water and stirred at room temperature. Evaluation for transparency is done visually. After the equilibrium is reached by a mixture, it is further titrated with aliquots of distilled water until it shows turbidity. Transparent and isotropic samples are suggested to be within the micro-emulsion region, and therefore, no more attempts are made to spot the other regions of the phase diagrams. Depending on these results, an appropriate percentage of oil, surfactant, and co-surfactants are selected. Concentrations are harmonized in the phase diagram and are applied for the preparation of SMEDDS.

Preparation of SMEDDS: Preparation of SMEDDS depends on

- The solubility of drugs in independent oil, surfactant, and co-solvent.

- The preferable choice of oil, surfactant and co-surfactant.
- Construction of phase diagram.
- The formulation is developed by mixing oil with a surfactant at 50-60 ºC. The drug is added to the oil phase and then dissolved into the mixture of surfactant and co-surfactant by steady stirring and kept at 50º to 60 ºC until a clear solution is obtained [25].

Evaluation of SMEDDS:

- ***In-vitro* Release Study:** *In-vitro* drug release study is performed by dialysis method, standard USP type II dissolution apparatus with paddle and diffusion cell. USP type II dissolution apparatus is kept at a rotating speed of 50 rpm maintained at a temperature of 37 ± 0.5 °C in dissolution media of pH 1.2 and 6.8 - to assess the effect of pH on drug release from SMEDDS. Formulation of liquid SMEDDS is filled in hard gelatine capsules. During the study 1 ml of sample aliquots are withdrawn at a predetermined time interval of 15, 30, 45, 60, and 120 min from the dissolution medium and immediately replaced with fresh buffer solution to maintain the sink condition of dissolution medium. Sample aliquots are filtered and diluted further for HPLC analysis or by UV-visible analysis to examine the amount of drug and release profile in dissolution media [26].
- **Droplet Size:** Brownian motion of droplets scatters light; fluctuations in the light scattering are measured by photon correlation spectroscopy, which is converted into particle size in the range of 3 nm to 3 µm. Laser diffractions evaluate the angular distribution of light scattered by the dilute sample and detect droplets from 0.5 nm to 200 µm. Nowadays, freeze-fracture electron microscopy is also used for the surface of the dispersed phase [27].
- **Zeta Potential Measurement:** Free fatty acids impart a negative charge to oil droplet, which can be measured by Zeta potential. Zeta potential is evaluated by using zeta sizer HSA 3000 (Malvern Instrument Ltd., UK). Clear, transparent, and disposable cuvettes are used for samples, and further results are reported. For every fresh sample, cuvettes are washed with the methanol and are rinsed using the sample to be assessed before each experiment [28].
- **Turbidity Evaluation:** Turbidometers are used to measure the turbidity of emulsion. Turbidity demonstrates the growth of emulsion. The turbidity of the resultant emulsions given in nephelometric turbidity units (NTU) is examined most frequently by Hach turbidity meter (Model 2100AN, Loveland, CO.) and the orbecohellle turbidity meter. With the help of turbidity meter, the turbidity can be measured by adding a specific amount of SMEDDS formulation in a suitable medium (0.1 N hydrochloric acid) under continuous agitating (50 rpm) on the magnetic plate at ambient temperature [29].
- **Liquefaction Time:** Liquefaction time determines the time taken by solid SEDDS / SMEDDS form to melt *in-vivo* without agitation at normal body temperature. The dosage form is covered with a transparent polyethylene film and tied to the bulb of a thermometer by means of a thread. The thermometer with fix attached dosage form is placed in a round bottom flask consisting of 250 ml of simulated gastric fluid maintained at 37 ºC. The time taken for liquefaction is noted [30].
- **Dispersibility Test:** Self emulsification ability of oral nano or micro-emulsion is examined by dispersibility test using USP dissolution apparatus II. Visual examination is done in the dissolution apparatus containing 1 mL of formulation and 500 mL of water set at 37 ± 0.5 ºC. Gentle stirring is provided by revolving apparatus at 50 rpm. The grading system is used to categorize the formation of a micro-emulsion (o/w or w/o), micro-emulsion gel, emulsion, or emulgel. The *in-vitro* production of the formulations is visually determined using the following grading system:
- **Grade A:** very quickly forming (within 1 min) nano-emulsion, having a transparent, clear or bluish appearance.

- **Grade B:** formulation containing a bluish-white appearance formed due to rapidly, slightly less clear emulsion formation.
- **Grade C:** Sublime milky emulsion that is formed within 2 min.
- **Grade D:** slow to emulsify (longer than 2 min) which contain dull, greyish-white emulsion having a slightly oily appearance
- **Grade E:** with large oil globules present on the surface of formulation which display either poor or minimal emulsification

Dispersion ability of nanoemulsion in GIT graded themselves into A and B while SEDDS are categorized into grade C [31].

- **Thermodynamic Stability Studies:** The inability of the drug to distribute itself in the mixture of excipients matrix can be tested by thermodynamic stability studies. Phase separation is a sign of physical instability which can be observed visually. Brittleness or deformation leads to retarded disintegration or insufficient drug release due to incompatibilities between the formulation and the gelatin capsules shell.

A. Heating Cooling Cycle: Prepared SMEDDS are subjected to continuous 6 cycles of refrigeration 4 ºC and heating 45 ºC. The holding period in each cycle should not exceed 48 hrs. After the specified holding period droplet size of diluted SMEDDS is examined by photon correlation spectroscopy. Visual inspection is also done for creaming or phase separation. A formulation which is stable to heating-cooling cycle with no separation of phases is subjected to centrifugation.

B. Centrifugation: Centrifugation is done at 3500 rpm for 30 min between the temperature ranges of 21 ºC to 25 ºC for not less than 48h. After centrifugation, formulations which do not show any sign of phase separation is processed for a freeze-thaw stress test.

C. Freeze-thaw cycle: Formulations which pass this test, exhibit better stability with no phase separation, creaming or cracking [32].

- **Viscosity Determination:** The self-micro emulsifying drug delivery system is usually administered in soft gelatin or in hard gelatin capsules. It can be quiet easily pourable into capsules, and such a system should not be too thick to create complications. With the help of Brookfield viscometer, the rheological properties of the micro-emulsions can be determined. If the system contains low viscosity when it is o/w type of the system and if high viscosities, then it is w/o type of the system [33].

- **Refractive Index:** The isotropic nature of micro-emulsion can be evaluated by the refractive index. The thermodynamic stability of the formulation can be manifested by a constant refractive index. Refractive indices are determined with the refract meters and are compared with the refractive index of water. It is dependent on the nature and amount of co-surfactant and the globule size of the formulation. Lower the rigidity of the micro-emulsions; lower is the refractive index.

- **Percent Transmittance:** The formulation is added in water and is inspected spectro-photometrically. If it displays results near to 100%, then it can be inferred as clear and transparent micro-emulsion [34].

- **Cloud Point Determination:** Stability assessment of micro-emulsion at body temperature can be evaluated by the cloud point. SMEDDS formulation containing 10 mg of the drug is diluted with 50 ml of distilled water in a beaker and kept in a water bath. The temperature of the beaker is then increased thoroughly until the SMEDDS formulation exhibits cloudiness [35].

- **Drug Content Measurement:** The drug content is evaluated by dissolving the micro-emulsion equivalent to a dose of the drug in 25 ml of methanol, mix properly with shaking for three to four times, and further dilution with the same solvent. Analyze drug content after appropriate dilution using a UV spectro-photometer or appropriate analytical technique by using methanol as a blank [36].

Dosage Forms of the Solid SMEDDS

Dry Emulsions: Conversion of classical liquid emulsion to dry form can solve the problem of instability of liquid dosage form. The spontaneous emulsion is formed when dry emulsion comes in contact with an aqueous solution of the GI tract. With the use of solid carriers (lactose, neusilin US2/UFL2, maltodextrin) in the aqueous phase of o/w emulsion, dry emulsion formulation can mostly be produced with the help of techniques such as rotary evaporation, freeze-drying or spray drying [37].

Capsules: S-SMEDDS can be converted to unit dosage form by filling into capsules. Degradation of the capsule in the GI tract releases S-SMEDDS, which spontaneously form micro-emulsion after coming into contact with the aqueous fluid of GIT. Recently supersaturated SMEDDS has been designed to avoid drug precipitation after dilution by GI fluid. For this purpose, polyvinylpyrrolidone (PVP) as well as hydroxypropyl methylcellulose (HPMC) or other water-soluble cellulosic polymers (methylcellulose, hydroxypropyl methylcellulose phthalate, and sodium carboxymethylcellulose) could be used in the formulations by creating and balancing supersaturated state *in-vivo* to reduce GI side effects. These formulations contain reduced amounts of surfactants. Solid SMEDDS are formulated by different techniques such as adsorption on the solid carriers, spray drying, *etc*. This also leads to the physical compatibility of liquid SMEDDS with the capsule shell [38].

Self-emulsifying Controlled / Sustained-release Tablets: The polymeric approach can be used to sustain the action of formed SMEDDS. Self-emulsifying OROS, carvedilol, and diclofenac tablets are few examples for sustained action of the prepared self-emulsifying dosage form. Self-emulsifying OROS containing elementary osmotic pump provides stable plasma concentration, controlled release rate, and increased bio-availability. S-SMEDDS of diclofenac is prepared using goat fat as a lipid and tween 65 as a surfactant. Sustained-release action of anti-hypertensive carvedilol is obtained when S-SMEDDS is converted to self-emulsifying tablets.

In order to significantly reduce the amount of solidifying excipients required for the trans-formation of SMEDDS into solid dosage forms, gelled SMEDDS have been developed. Colloidal silicon dioxide (Aerosil 200) was selected as a gelling agent for the oil-based systems, which serve the dual purpose of reducing the required amount of solidifying excipients and also aids in slowing down of the drug release. Liquid SMEDDS could be adsorbed on to porous carriers in various proportions. The surface adsorbed liquid SMEDDS is then mixed with other suitable excipients. The mixture is further compressed by utilizing a compression machine. Within the formulation, the eutectic based self-emulsifying tablets inhibit the irreversible precipitation of the drug [39].

Self-emulsified (SE) Sustained / Controlled Release Pellets: Some recent findings consist of Self emulsified controlled-release pellets formed by consolidating drugs into SES/CP, thereby resulting into the sustained or controlled release of the drug, in contrast with coated pellets with a water-insoluble polymer that reduce the rate of drug release. Pellets are convenient multiple unit dosage forms, which are formulated by extrusion/spheronization techniques. Glyceryl palmito-stearate (Gelucire 54/02) labrafil M1944CS, CMS-Na, microcrystalline cellulose, glyceryl behenate (Gelucire 70/02) and α lactose monohydrate, can be used to formulate SE sustained-release matrix pellets [40].

TABLE 2: LITERATURE UPDATES ON DIFFERENT REPORTS OF TYPE III LFCS DESIGNED FOR THE ORAL DELIVERY OF LIPOPHILIC DRUGS

SMEDDS	Silymarin	Ethyl linoleate	Tween 80:transcutol P	Relative bioavailability of SMEDDS was enhanced to an average of 1.88 and 48.82 folds that of silymarin PEG 400 solution and suspension, respectively.
SMEDDS	N-442	L-ascorbic acid	Gelucire®:HCO 60®	Rapid self micro emulsification in various aqueous media, and formed stable microemulsion with a mean droplet size of about 20 nm.
SMEDDS	Lovastatin	Sunflower oil	Acrysol K 140: capmul MCM	It provides better drug solubilization, drug stability in water and 0.1 mol/l HCL. Also improved *in-vitro* release of lovastatin compared to the marked product.
SMEDDS	Tacrolimus	Capmul MCM C8	Cremophore EL: carbitol	It was superior to marketed pangraf capsules formulation with respect to *in-vitro* dissolution profile and *in-vivo*

				immunosuppressant activity.
SMEDDS	Bicalutamide	Caproyl PGMG	Polyethelene:cremophore RH glycol 30040	2 fold increase in bioavailability compared to suspension formulation.
SMEDDS	Furosemide	miglyol	Labrasol: plurol oleique	Core of microcapsules resulted in improved permeability and drug release characteristics in comparison to microspheres.
SMEDDS	Halofentine	Captex	Cremophore EL: ethanol	6-8 fold higher bioavailability than solid Halofentine HCL tablet formulation.
SMEDDS	B-artemether	N-LCT	Cremophore EL: ethanol	Resulted in significant improvement of the anti-malarial activity as compared to that of larither®
SMEDDS	Sulpiride	Oleic acid	Tween 80: propylene glycol	The permeability coefficient was higher with the SMEDDS and micellar solutions containing sulpiride across all the intestinal segments compared to the drug solution.
SMEDDS	Docetaxel	tetraglycol	Cremophore ELP: labrasol	Docetaxel-loaded SMEDDS showed an inhibitory effect on B16F10 melanoma proliferation.
SMEDDS	Pueraria lobata	Ethyl oleate	Tween 80: transcutol P	2.5 fold higher bioavailability than conventional tablets.
SMEDDS	Bufalin	Maisine 35-1 miglycol 812M	Cremophore EL: trancutol	2.38 fold higher bioavailability than bufalin suspension.
SMEDDS	Rapamycin	MCT	CremophorRH 40: Transcutol P Glycerol	1.5-2.5 fold higher bioavailability than oral solution Rapamune
SMEDDS	Valsartan	Campul MCM	Tween 80: PEG 400	1.78 fold times higher bioavailability than conventional capsule formulation
SMEDDS	Silybin	Ethyl lioleate	Cremophor RH 40: Transcutol P Glycerol	2.3 fold higher bioavailability than hard capsule
SMEDDS	Sorafenib	Ethyl oletate	Cremophor EL : PEG 400	25 times higher bioavailability than suspension
SMEDDS	Nifedipine	Seasome oil	Span 80/ Tween 80: n-butanol	4-5.5 fold higher bioavailability than pure drug
SMEDDS	Glyburide	Capryol 90	Tween 20: transcutol P	It improves the dissolution rate of glyburide compared to the marketed formulation and pure glyburide powder.
SMEDDS	Oridonin	Labracfac Cc and maisine 35-1	Cremophore EL: transcutol P	Improved bioavailability with 2.2 fold higher than suspension
SMEDDS	Celecoxib	Acconon MC-8	Tween 20: capmul PG	Relative bioavailability of the SMEDDS formulation to the conventional capsule was 132%
SMEDDS	finofibrate	labrafac CM 10	Tween 80: peg 400	SMEDDS formulation higher oral bioavailability as compared to with plain finofibrate.
SMEDDS	Simvastatin	Capryol 90	Cremophore EL: carbitol	Increase in 1.5 fold bioavailability higher than conventional tablets
SMEDDS	nimodipine	Ethyl oleate	cremophore® RH 40: labrasol®	HPMC used as control release and enhanced the bioavailability
SMEDDS	Xibornol	Labrafil M 1944	Labrasol: transcutol P	Stable liquid SMEDDS which permitted the introduction of relatively high concentration (3% w/v) of xibornol in the form of solution.
SMEDDS	Exemestane	Capryol 90	Cremophore ELP: transcutol HP	It enhances the dissolution of exemestane.
SMEDDS	Oridonin	Labrafac CC and maisine 35-1	Cremophore EL: transcutol P	A rapid release with approximately 26% released at the first 10 min.
SMEDDS	Ligusticum chuanxiong oil	Chuanxiong oil	Tween 80: propylene glycol	The absorption rate was 2.13 and 1.59 times higher than that of VOC and VOC/â-CD
SMEDDS	Seocalcitol	Viscoleo	Cremophore	The simple lipid solution of Seocalcitolseem to be superior for

			RH40: akoline MCM	the formulation of seocalcitol compared with the corresponding more advanced SMEDDS developed in the present study
SMEDDS	vinpocetine	Ethyl oleate	Solution HS 15: transcutol ® P,	1.72 folds higher bioavailability than the commercial tablets.
SMEDDS	Acyclovir	Sunflower oil	Tween 60: glycerol	3.5 higher bioavailability than the pure drug solution.
SMEDDS	Buparvaquone	Capryol 90	Cremophore EL: LABRASOL	Increases the rate and extent of absorption.
SMEDDS	Curcumin	Ethyl oleate	Cremophore EL: PEG 400 emulsifier OP	Improved bioavailability with 3.86 times higher than the curcumin
SMEDDS	Paclitaxel	Vit E	Cremophore EL: ethanol	Increase in 5 fold bioavailability and c max 10 fold higher than orally Taxol® formulation.
SMEDDS	carvedilol	Gelucire 44/14	Lauroglycol 90: oleylamine	Enhanced its absorption without interaction or incompatibility between the ingredients.

Methods of Solidification Techniques for Transforming Liquid /Semisolid SMEDDS to S-SMEDDS: [41, 42]

Melt Extrusion / Extrusion Spheronization: This is a solvent-free process which can load up to 60% of drug and can give better content uniformity than other methods. Materials with the plastic flow can be extruded to get uniform shaped spheroids under controlled temperature, pressure, and flow rate. The extrusion process is used extensively in the pharmaceutical field to formulate pellets. Pelletization process involves the mixing of API and excipients, converting dry homogenous mixture to wet mass by using a binder, the formation of spaghetti-like extrudate through the extrusion process, and lastly, spheronization of extrudates.

Melt Granulation: Melt granulation is a solvent-free process where binders which gets soften at a relatively lower temperature, are used. The addition of liquids to form granules and subsequent drying of wet granules is not required in melt granulation process. In this method, impeller speed, viscosity, mixing time, the concentration of binder and particle size of the binder are major granulation process parameters. Binders with low melting temperatures include Gelucire, a family of a vehicle containing mixtures of mono/di/triglycerides, PEG esters of fatty acids, and lecithin has been tested for melt granulation.

Adsorption to Solid Carriers: It is a simple and economical process. The liquid self-emulsifying formulation can be converted to free-flowing powder by adsorbing on to solid carriers. The formed solid powders can be filled into capsule or can be compressed into a tablet dosage form. Adsorption results in content uniformity. Solid carriers used for adsorption include materials that have high surface areas like sodium carboxymethyl cellulose, crosslinked polymethyl methacrylate, silicates, silica, magnesium trisilicate, magnesium hydroxide, talcum, and crospovidone. Recently porous silicon dioxide (Sylysia 550), carbon nanotubes, bamboo charcoal, carbon nanohorns, fullerene and charcoal are used as nanoparticle adsorbents.

Spray Drying: A mixture of drugs, lipids, surfactants, and solid carriers are either solubilized or suspension is prepared. The prepared suspension is then sprayed using a spray dryer. Solubilized liquid formulation mixture is atomized into a spray of droplets. Further droplets are developed into the drying chamber, which leads to evaporation of the volatile phase (water content from the emulsion), producing the dry particles under controlled airflow conditions and temperature. The resulting fine particles can be utilized for the preparation of tablets and capsules. As per the drying characteristics of the product and powder specifications, the selection of parameters such as drying chamber design, suitable airflow pattern, temperature, and the atomizer are considered.

Capsule Filling: Capsule filling is economical and most widely used technology for encapsulation of liquid or semisolid self-emulsifying formulations. Semisolids are filled into capsules in four different steps, heating semisolid excipients above its melting point, stirring active substrate with

excipients, filling of capsule with molten mixture, allowing cooling to room temperature, followed by sealing the body and cap either by banding or by micro spray sealing. For the drugs which are poorly insoluble or compounds like proteins and peptides, recent advancements in capsule technology such as liquid Oros technology (Alza Corporation) has been designed for controlled delivery. The working principle of this system is based on osmotic and liquid self-emulsifying formulation system. It involves an osmotic layer, which expands after contact with the water and pumps the drug formulation through small orifice present in the hard or soft capsule.

In capsule filling, the primary consideration evaluated is compatibilities between the excipients and capsule shell. Most of the semisolid or liquid lipophilic vehicles are compatible with hard capsules.

Recent Patents of SMEDDS:

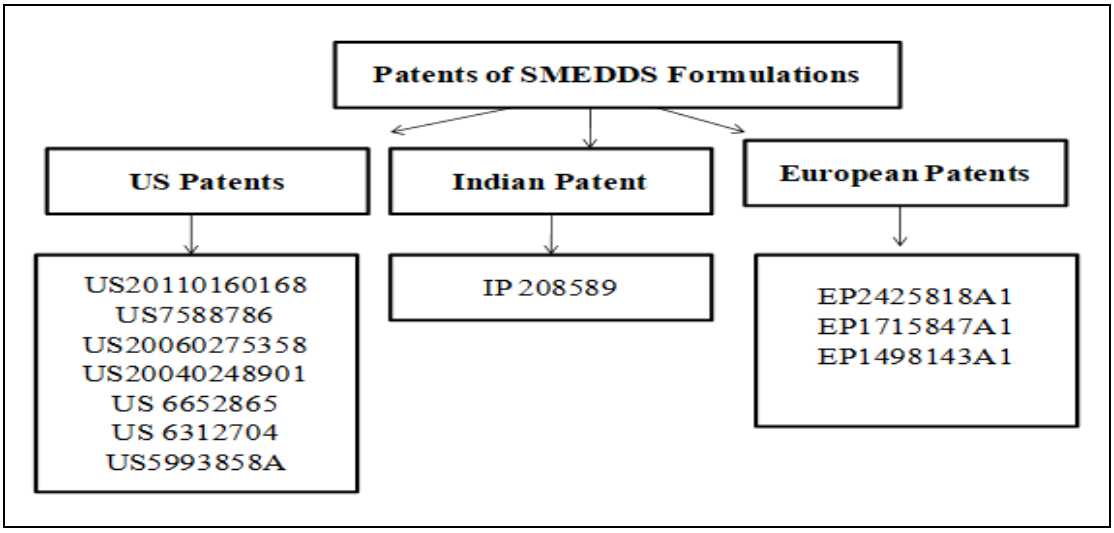

FIG. 1: PATENTS OF SMEDDS FORMULATIONS

TABLE 3: EXAMPLES OF EXCIPIENTS USED IN SMEDDS

Trade name	Chemical name
Lipids	
Vegetable oil Castor oil, olive oil, sunflower oil, soybean oil, cod-liver oil, Arachis oil, peanut oil, oleic acid, cottonseed oil, cinnamon oil	Long-chain TAG
Miglyol 812	Medium-chain TAG caprylic/ capric TAG
Labrafac Lipophile WL 1349	Medium-chain triglycerides [Caprylic (C8) 50–80%, Capric (C10) 20–50%]
Isopropyl myristate	FA ester
Labrafac PG	PG dicaprylocaprate
Maisine 35-1	Glyceryl mono-linoleate
Capryol 90	Propylene glycol monocaprylate
Lauroglycol 90	Propylene glycol monolaurate
Lauroglycol FCC	Propylene glycol monolaurate
Capmul MCM C8	Glyceryl Monocaprate Type 1
Surfactants	
Labrafil M1944CS	Oleoyl macrogol glycerides
Lauroglycol 90	PG monolaurate
Cremophor EL	Polyoxyl 35 castor oil
Labrasol	Caprylocaproyl macrogol glycerides
Polysorbate 80/Tween 80	Polyoxyethylene (20) sorbitan monooleate
Polysorbate 20/Tween 20	Polyoxyethylene (20) sorbitan monolaurate
Co-surfactatns	
Propylene glycol PEG	PEG 300 and PEG 400
Transcutol	Transcutol HP and P [Diethyl glycol monoethyl ether]

CONCLUSION: SMEDDS is a promising drug delivery system for improving and increasing the bioavailability of drugs compounds with poor aqueous solubility, having high molecular weight, enzymatic degradation, pre systemic first-pass effect, gastric irritation, low bioavailability, and limited dissolution rate. As discussed, SMEDDS and SSMEDDS are substitute novel drug delivery systems superior to conventional dosage forms, which result in the least production cost, simple manufacturing scale-up for industries, better patient compliance, and improved stability. While designing this formulation, it is very important to understand the role of independent lipids, surfactants, and co-surfactants in the formation of SMEDDS, with a preview of the dispersion process, drug solubilization and the structure of the formed emulsion. This review article will definitely help to explore the probabilities of loading a wide variety of hydrophobic drugs in SMEDDS AND SSMEDDS as their scale-up is convenient as well as economical too.

ACKNOWLEDGEMENT: Authors doesn't want to acknowledge.

CONFLICTS OF INTEREST: None

REFERENCES:

1. Deokate UA, Shinde NI and Bhingare U: Novel approaches for development and characterization of SMEDDS. International Journal of Current Pharmaceutical Research 2013; 5(4): 5-12.
2. Rahman MA, Hussain A, Hussain MS, Mirza MA and Iqbal Z: Role of excipients in successful development of self-emulsifying / microemulsifying drug delivery system (SEDDS/SMEDDS). Drug Development and Industrial Pharmacy 2013; 39(1): 1-9.
3. Dokania S and Joshi AK: self-microemulsifying drug delivery system (SMEDDS)–challenges and road ahead. Drug Delivery 2015; 22(6): 675-90.
4. Pouton CW: Lipid formulations for oral administration of drugs: non-emulsifying, self-emulsifying and self-micro-emulsifying drug delivery systems. European Journal of Pharmaceutical Sciences 2000; 11(2): 93-8.
5. Kyatanwar AU, Jadhav KR and Kadam VJ: Self micro-emulsifying drug delivery system (SMEDDS). Revised Journal of Pharmacy Research 2010; 3: 75-83.
6. Mittal P, Seth N and Rana AC: Self-microemulsifying drug delivery system (SMEDDS): An alternative approach for hydrophobic drugs. International Journal of Natural Product Science 2012; 1: 80.
7. Misal RS, Potphode VR and Mahajan VR: Review On: New approaches in self micro-emulsifying drug delivery system. Res J of Pharm and Techno 2017; 10(4): 1215.
8. Agrawal S, Giri TP, Tripathi Dl, Ajazuddin and Alexander A: A review on novel therapeutic strategies for the enhancement of solubility for hydrophobic drugs through lipid and surfactant based self micro emulsifying drug delivery system: a novel approach. American Journal of Drug Discovery and Development 2012; 2(4): 143-83.
9. Porter CJ, Charman WN: *In-vitro* assessment of oral lipid based formulations. Advanced Drug Delivery Reviews 2001; 50 (1): S127-47.
10. Porter CJ and Charman WN: Intestinal lymphatic drug transport: an update. Advanced. Drug Delivery Reviews 2001; 50(1-2): 61-80.
11. Lo YL, Hsu CY and Huang JD: Comparison of effects of surfactants with other MDR reversing agents on intracellular uptake of epirubicin in caco-2 cell line. Anticancer Research 1998; 18(4C): 3005-9.
12. Yu L, Bridgers A, Polli J, Vickers A, Long S, Roy A, Winnike R and Coffin M: Vitamin E-TPGS increases absorption flux of an hiv protease inhibitor by enhancing its solubility and permeability. Pharmaceutical Research 1999; 16(12): 1812-7.
13. Craig D: The use of self-emulsifying systems as a means of improving drug delivery. Bulletin Technique-Gattefosse 1993: 21-32.
14. Reiss H: Entropy-induced dispersion of bulk liquids. Journal of Colloid and Interface Science 1975; 53(1): 61-70.
15. Gao P: Design and development of self-emulsifying lipid formulations for improving oral bioavailability of poorly water-soluble and lipophilic drugs. In formulating poorly water soluble drugs. Springer, New York, NY 2012: 243-266.
16. Gao P and Morozowich W: Development of super-saturatable self-emulsifying drug delivery system formulations for improving the oral absorption of poorly soluble drugs. Expert Opinion on Drug Delivery 2006; 3(1): 97-10.
17. Land LM, Li P and Bummer PM: The influence of water content of triglyceride oils on the solubility of steroids. Pharmaceutical Research 2005; 22(5): 784-8.
18. Kovvasu S, Kunamaneni P, Joshi R and Betageri G: Self-emulsifying drug delivery systems and their marketed products: a review. Asian Journal of Pharmaceutics 2019; 13(2): 73.
19. Shinoda K and Lindman B: Organized surfactant systems: microemulsions. Langmuir 1987(2): 135-49.
20. Singh B: Development of optimized self-nano-emulsifying drug delivery systems (SNEDDS) of carvedilol with enhanced bioavailability potential. Drug Delivery 2011; 18(8): 599-12.
21. Ranpise AA and Wagh MP: Lipid-based self-micro-emulsifying drug delivery system: A novel approach for lipophilic drugs. Journal of Pharmacy Research 2018; 12(4): 560.
22. Akula S, Gurram AK and Devireddy SR: Self-micro-emulsifying drug delivery systems: An attractive strategy for enhanced therapeutic profile. International Scholarly Research Notices 2014; 1-11.
23. Jain NK: Progress in Controlled and Novel Drug Delivery System: CBS Publication and Distributors 2004: 309-340.
24. Ingle LM, Wankhade VP, Udasi TA, Tapar KK: New approaches for development and characterization of SMEDDS. International Journal of Pharmacy and Pharmaceutical Science Research 2013; 3(1): 7-14.
25. Do Thi T, Van Speybroeck M, Barillaro V, Martens J, Annaert P, Augustijns P, Van Humbeeck J, Vermant J and Van Den Mooter G: Formulate-Ability of Ten Compounds with Different Physicochemical Profiles in SMEDDS. European Journal of Pharmaceutical Sciences 2009; 38(5): 479-88.

26. Kang BK, Lee JS, Chon SK, Jeong SY, Yuk SH, Khang G, Lee HB and Cho SH: Development of Self-Micro-emulsifying Drug Delivery Systems (SMEDDS) for Oral Bioavailability Enhancement of Simvastatin in Beagle Dogs. International Journal of Pharmaceutics 2004; 274(1-2): 65-73.
27. Vyas SP and Khar RK: Submicron emulsion. in: targeted and controlled drug delivery novel carriers systems. India: CBS Publishers and Distributors 2002: 291–94.
28. Patel MJ, Patel SS, Patel NM and Patel MM: A Self-Microemulsifying Drug Delivery System (SMEDDS). Int Journal of Pharma Science Rev Res 2010; 4(3): 29-35.
29. Nazzal S, Smalyukh II, Lavrentovich OD and Khan MA: Preparation and *in-vitro* characterization of a eutectic based semisolid self-nanoemulsified drug delivery system (SNEDDS) of ubiquinone: mechanism and progress of emulsion formation. International Journal of Pharma-ceutics 2002; 235(1-2): 247-65.
30. Attama AA, Nzekwe IT, Nnamani PO, Adikwu MU and Onugu CO: The Use of Solid Self-Emulsifying Systems in The Delivery of Diclofenac. International Journal of Pharmaceutics 2003; 262(1-2): 23-8.
31. Tiwari N, Chopra H, Sagar M and Sharma AK: A review on self emulsified drug delivery system: a promising approach for drug delivery of bcs class II and IV drugs. Journal of Pharmaceutical Research 2016; 15(4): 181-8.
32. Cui J, Yu B, Zhao Y, Zhu W, Li H, Lou H and Zhai G: Enhancement of oral absorption of curcumin by self-microemulsifying drug delivery systems. International Journal of Pharmaceutics 2009, 371 (1-2): 148-155
33. Potphode VR, Deshmukh AS and Mahajan VR: Self-micro emulsifying drug delivery system: an approach for enhancement of bioavailability of poorly water soluble drugs. Asian J of Pharm and Techn 2016; 6(3): 159-68.
34. Gautam P and Shastri D: Self-micro-emulsifying drug delivery system to enhance the solubility of the hydrophobic drugs. Current Trends Biomedical Engineering and Biosciences 2018; 13(4): 555867.
35. Khade S and Pore Y: Formulation and evaluation of neusilin us 2 adsorbed amorphous solid self micro emulsifying delivery system of atorvastatin calcium. Asian Journal of Pharma and Clinical Research 2016; 9(4): 1-8.
36. Deshmukh A, Nakhat P and Yeole P: Formulation and *in-vitro* evaluation of self microemulsifying drug delivery system (SMEDDS) of Furosemide. Der Pharm Lett 2010; 2(2): 94-106.
37. Christensen KL, Pedersen GP and Kristensen HG: Preparation of redispersible dry emulsions by spray drying. International Journal of Pharma 2001; 212(2): 187-94.
38. Gao P and Morozowich W: Development of supersaturatable self-emulsifying drug delivery system formulations for improving the oral absorption of poorly soluble drugs. Expert Opinion on Drug Delivery 2006; 3(1): 97-10.
39. Ravichandiran V, Masilamani K. Kumar SS and Lavakumar V: Bioavailability of poorly water soluble drugs: self emulsifies drug delivery systems: A Novel Approach. International Journal of Pharmaceutical Sciences Review and Research. 2011; 10(2): 72-77.
40. Serratoni M, Newton M, Booth S and Clarke A: Controlled drug release from pellets containing water-insoluble drugs dissolved in a self-emulsifying system. Euro Journal of Pharma and Biopharmaceutics 2007; 65(1): 94-8.
41. Tang B, Cheng G, Gu JC and Xu CH: Development of solid self-emulsifying drug delivery systems: preparation techniques and dosage forms. Drug Discovery Today 2008; 13(13-14): 606-12.
42. Sharma VK, Koka A, Yadav J, Sharma AK and Keservani RK: Self-micro emulsifying drug delivery systems: a strategy to improve oral bioavailability. Ars Pharm 2016; 57(3): 97-09.

How to cite this article:
Shelar A, Mahore J, Deshkar S and Trivedi R: Improvement in bioavailability of poorly soluble drug by self micro emulsifying drug delivery. Int J Pharm Sci & Res 2020; 11(8): 3595-07. doi: 10.13040/IJPSR.0975-8232.11(8).3595-07.